FDA Briefing Document

Pharmacy Compounding Advisory Committee (PCAC) Meeting

October 29, 2024

The briefing packages for L-theanine, Ibutamoren mesylate, Ipamorelin-related bulk drug substances (Ipamorelin (free base) and Ipamorelin acetate), Kisspeptin-10, and Hydroxyprogesterone caproate topics contains background information prepared by the Food and Drug Administration (FDA or Agency) for the panel members of the Pharmacy Compounding Advisory Committee (advisory committee). We are bringing certain compounding issues to this advisory committee to obtain the advisory committee's advice. The background package may not include all issues relevant to the final committee recommendation and instead is intended to focus on issues identified by the Agency for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

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I. Introduction

Section 503A of the Federal Food, Drug, and Cosmetic Act (FD&C Act) describes the conditions that must be satisfied for human drug products compounded by a licensed pharmacist in a State-licensed Pharmacy or Federal facility, or by a licensed physician, to be exempt from the following three sections of the FD&C Act: section 505 (concerning the approval of drugs under new drug applications (NDAs) or abbreviated new drug applications (ANDAs)); section 502(f)(1) (concerning the labeling of drugs with adequate directions for use); and section 501(a)(2)(B) (concerning current good manufacturing practice (CGMP) requirements).

A. Bulk Drug Substances That Can Be Used by Compounders under Section 503A

One of the conditions that must be met for a compounded drug product to qualify for the exemptions in section 503A of the FD&C Act is that a licensed pharmacist or licensed physician compounds the drug product using bulk drug substances that:

(1) Comply with the standards of an applicable United States Pharmacopeia (USP) or National Formulary (NF) monograph, if a monograph exists, and the USP chapter on pharmacy compounding;
(2) If such a monograph does not exist, are drug substances that are components of drugs approved by the Secretary; or
(3) If such a monograph does not exist and the drug substances are not components of drugs approved by the Secretary, appear on a list developed by the Secretary through regulations issued by the Secretary under subsections (c) of section 503A (the 503A Bulks List).

(*See* section 503A(b)(1)(A)(i) of the FD&C Act.)

1. *Process for Evaluating Bulk Drug Substances Nominated for Inclusion on the 503A Bulks List*

FDA is considering substances for inclusion on the 503A Bulks List. In the *Federal Register* of February 19, 2019 (84 FR 4696), FDA published notice of a final rule establishing the criteria for evaluation of bulk drug substances for inclusion on the 503A Bulks List:

(1) The physical and chemical characterization of the substance;
(2) Any safety issues raised by the use of the substance in compounded drug products;
(3) The available evidence of the effectiveness or lack of effectiveness of a drug product compounded with the substance, if any such evidence exists; and
(4) Historical use of the substance in compounded drug products, including information about the medical condition(s) the substance has been used to treat and any references in peer-reviewed medical literature.

In evaluating bulk drug substances for the 503A Bulks List under these criteria, FDA will use a balancing test. Specifically, the Agency will consider each criterion in the context of the others

and balance them, on a substance-by substance basis, to evaluate whether a particular substance is appropriate for inclusion on the list.

2. *Bulk Drug Substances Under Evaluation for Inclusion on the 503A Bulks List*

The Agency is considering L-theanine, Ibutamoren mesylate, Kisspeptin-10, and Ipamorelin-related bulk drug substances (Ipamorelin (free base) and Ipamorelin acetate) for inclusion on the 503A Bulks List. See links provided below for the background material that forms the basis for FDA's proposals regarding these bulk drug substances.

B. Withdrawn or Removed List

1. *Process for Identifying Candidates for or Amendments to the Withdrawn or Removed List*

Under sections 503A and 503B of the FD&C Act, FDA is to develop a list of drugs that have been withdrawn or removed from the market because they have been found to be unsafe or not effective (the Withdrawn or Removed List (codified at 21 CFR § 216.24)).

The following outlines the process that has been and will be used in the future to identify new candidates for this list, or to identify proposed amendments to the list, such as removing an entry or amending an entry on the list to qualify it in some way because the drug has been shown to be safe and effective for some use.

FDA stated in a final rule published in the October 7, 2016 *Federal Register* that FDA intends to continue updating the Withdrawn or Removed List through notice and comment rulemaking (s*ee* 81 FR 69668).

Process for Identifying Candidates for Amendments to the List:

- FDA periodically reviews available information to identify and compile a list of possible new candidate drugs that have been withdrawn or removed from the market because they have been found to be unsafe or not effective. The information may include, for example, *Federal Register* notices announcing withdrawal of approval of a drug application for safety or effectiveness reasons, *Federal Register* notices announcing an Agency determination that a drug product was removed from sale for reasons of safety or effectiveness, relevant FDA Alerts, FDA Drug Safety Communications, FDA News Releases, Public Health Advisories, Dear Healthcare Practitioner Letters, Citizen Petitions, and Sponsor Letters.

- In addition, periodically, FDA reviews available information to determine whether any new drug applications have been approved for a drug product containing as an active ingredient any of the drugs on the list to determine whether any of the drug entries on this list should be modified to account for this new safety and effectiveness determination and approval. For example, if a drug has been approved in a new formulation, indication, route of administration or dosage form since the list was last revised, FDA might consider proposing

a modification to the list to remove the drug from the list or to exclude the particular formulation, indication, route of administration or dosage form.

- Appropriate divisions within the Office of New Drugs (OND) then evaluate each identified candidate or proposed modification using the available information about the drug and prepare a review of the information that documents their recommendations as to whether to include the drugs on the Withdrawn or Removed List or remove a drug or modify an entry.

- We intend to propose regulations to revise the Withdrawn or Removed List periodically, as appropriate, as we identify drugs that we tentatively determine should be added to the list. We would also propose regulations when we tentatively determine that changes to the status of drug products already on the list should result in a revision to their listing; for example, if some version of a drug on the list has been approved for marketing.

2. *Drugs Under Evaluation for the Withdrawn or Removed List*

The Agency is considering "Hydroxyprogesterone caproate: All drug products containing hydroxyprogesterone caproate to reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth." See link provided below for the background material that forms the basis for FDA's proposal to include this drug on the list.

II. Substances Nominated for Inclusion on the 503A Bulks List (in order of discussion at the meeting)

A. L-theanine

1. FDA Evaluation

2. Nominations
   a. Wells Pharmacy Network

B. Ibutamoren mesylate

1. FDA Evaluation

2. Nominations
   a. LDT Health Solutions, Inc. on behalf of International Peptide Society
   b. Wells Pharmacy Network

3. Nomination Clarification
   a. Wells Pharmacy Network

C. Ipamorelin-related bulk drug substances (Ipamorelin (free base) and Ipamorelin acetate)

1. FDA Evaluation

2. Nominations
   a. LDT Health Solutions, Inc. on behalf of International Peptide Society[1]
   b. Wells Pharmacy Network[2]

D. Kisspeptin-10

1. FDA Evaluation

2. Nominations
   a. Wells Pharmacy Network

3. Nomination Clarification
   a. Wells Pharmacy Network

III. Drug Considered for the Withdrawn or Removed List

A. Hydroxyprogesterone caproate

1. FDA Evaluation

IV. Points to Consider

A. October 29, 2024, a.m. session

Points for the PCAC to Consider Regarding Whether FDA should Include Certain Bulk Drug Substances on the 503A Bulks List

[1] This nomination was withdrawn by the nominator (FDA-2015-N-3534-0472). However, FDA is electing to proceed with the presentation of ipamorelin-related bulk drug substances (ipamorelin (free base) and ipamorelin acetate) to the PCAC.
[2] This nomination was withdrawn by the nominator (FDA-2015-N-3534-0471). However, FDA is electing to proceed with the presentation of ipamorelin-related bulk drug substances (ipamorelin (free base) and ipamorelin acetate) to the PCAC.

1. FDA is proposing that L-theanine NOT be included on the 503A Bulks List.

2. FDA is proposing that Ibutamoren mesylate NOT be included on the 503A Bulks List.

B. October 29, 2024, p.m. session

Points for the PCAC to Consider Regarding Whether FDA should Include Certain Bulk Drug Substances on the 503A Bulks List

3. FDA is proposing that Ipamorelin (free base) NOT be included on the 503A Bulks List.

4. FDA is proposing that Ipamorelin acetate NOT be included on the 503A Bulks List.

5. FDA is proposing that Kisspeptin-10 NOT be included on the 503A Bulks List.

Points for the PCAC to Consider Regarding Whether FDA should Include Certain Bulk Drug Substances on the Withdrawn and Removed List

6. FDA is proposing that "Hydroxyprogesterone caproate: All drug products containing hydroxyprogesterone caproate to reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth" be ADDED to the Withdrawn or Removed List under sections 503A and 503B of the FD&C Act.